

EXHIBIT I



To freeze or not to freeze: decision regret and satisfaction following elective oocyte cryopreservation

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Objective: To characterize the degree of decision regret following elective oocyte cryopreservation (EOC) for social indications, and identify factors associated with regret.

Design: Retrospective cohort survey study.

Setting: Academic center.

Patients: Two hundred one women who underwent EOC for fertility preservation between 2012 and 2016.

Interventions: None.

Main Outcome Measures: Decision Regret Scale (DRS) score, from 0–100, with a cut-off >25 indicative of moderate to severe regret; and attitudes regarding decision satisfaction.

Results: Median DRS score was 0 (interquartile range 0–15) and the mean was 10 (range 0–90). Thirty-three women (16%) experienced moderate to severe decision regret. Factors associated with decision regret included: number of eggs frozen, perceived adequacy of information prior to EOC, adequacy of emotional support during EOC, and patient-estimated probability of achieving a live birth using their banked eggs. In a multivariate logistic model, increased perceived adequacy of information (adjusted odds ratio 0.63, 95% confidence interval 0.42–0.97) and patient-estimated probability of achieving a live birth (adjusted odds ratio 0.80, 95% confidence interval 0.67–0.96) were associated with reduced odds of regret. One hundred sixty-seven women (88%) reported increased control over reproductive planning following EOC. One hundred eighty-three (89%) affirmed they will be happy they froze eggs, even if they never use them.

Conclusions: The risk of decision regret following EOC is non-negligible. Low number of mature oocytes cryopreserved is a risk factor for increased regret, while perceptions of adequate information and emotional support, and increased patient-estimates of achieving a live birth using banked eggs are associated with reduced risk of regret. (Fertil Steril® 2018;109:1097–104. ©2018 by American Society for Reproductive Medicine.)

Key Words: Elective oocyte cryopreservation, social egg freezing, fertility preservation, decision regret

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The American Society for Reproductive Medicine (ASRM) retracted the experimental designation from oocyte cryopreservation for medical indications in 2012 (1). Subsequently there has been a rapid increase in utilization of this technology (2). In 2015 in the U.S., 7,518 oocyte banking

cycles were reported, twice that of 2012 (2). While some of these cycles represent fertility preservation for medical indications such as cancer, a major driver of the increased volume involves reproductively healthy women pursuing fertility preservation for social indications (3).

Use of elective oocyte cryopreservation (EOC) to circumvent age-related fertility decline is one marker of a greater societal trend to delay age of childbearing (4), often attributed to women's pursuit of educational, personal or professional goals (5–8). Proponents of EOC conceptualize the technology as bridging the gap between social opportunities outpacing biological realities (9).

Oocyte cryopreservation for non-medical reasons is a new application of egg-freezing technology, is completely elective, and there are limited data to help women anticipate the long-term reproductive outcomes of their decisions (10). Citing lack of efficacy data as well

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as concerns over unknown emotional risks, the current position of the ASRM is that, "...data ... are insufficient to recommend elective oocyte cryopreservation" (1). Given that this application is being widely employed despite this warning, it is critical to begin to study the quality of these important family planning decisions.

Decision regret has been defined as a negative emotion involving distress or remorse following a decision (11). It is considered an overall indicator of the quality of health decisions and is increasingly viewed as an important patient-reported outcome in interventional studies (12, 13).

Evidence regarding decision regret outcomes following EOC is sparse. A survey study of 183 women who underwent EOC in New York City from 2005 to 2011 found that 53% deemed the experience as empowering (9) but did not examine regret per se. Among 65 women who underwent EOC in Belgium from 2009 to 2011, none reported regretting egg banking; meanwhile, 3 of 29 women who sought consultation but did not pursue EOC reported regretting their decision (14). Ninety-five percent of oocyte bankers reported they would to do it again (14). Importantly, there are no published data assessing decision regret using a validated instrument. Furthermore, no decision outcomes data are available from women pursuing EOC in the modern paradigm in which oocyte cryopreservation technology is not considered experimental.

The objective of our study was to delineate the extent to which women electing oocyte cryopreservation for non-medical indications regret their decision, and to identify risk factors associated with decision regret. We additionally sought to characterize subjective attitudes of satisfaction following EOC to facilitate a balanced, comprehensive understanding of patient reflections on their EOC decision. We hypothesized that the following factors would be associated with decision regret: lower number of oocytes cryopreserved, reduced patient-estimated probability of achieving a live birth with their frozen eggs, reduced patient-estimated probability of returning to use their eggs to achieve pregnancy, lack of employer coverage of treatment expenses, lower perceived adequacy of information prior to undergoing EOC, lower perceived adequacy of emotional support during the EOC process, and ambivalent attitudes regarding the desire for parenthood.

MATERIALS AND METHODS

From 2012 to 2016, 503 women underwent EOC at a single academic institution. Women who froze eggs for medical indications (e.g. a new cancer diagnosis anticipating gonadotoxic therapy), for oocyte donation, and those intending in vitro fertilization but without available sperm on the day of egg retrieval were not included in the study cohort.

Following Institutional Review Board approval, a survey was distributed via email to the study cohort using a secure online REDCap platform (Vanderbilt University). Participants provided electronic signatures indicating consent to participate.

The primary outcome of our study, decision regret, was measured using the validated Decision Regret Scale (DRS) (11). The DRS was developed by a group of decision scientists and health practitioners. The validation process for the scale has been explicitly described (11), and involved testing in a

series of four patient populations making distinct health care decisions. Correlations of DRS scores with multiple measures (satisfaction, decisional conflict, and health outcomes) were examined to determine convergent validity (11). The DRS has been used broadly in the literature to assess decision regret across a variety of health care settings (12).

Additional questions specific to the experience of oocyte cryopreservation were developed by a panel of experts, including reproductive endocrine and mental health specialists, following literature review and exploratory qualitative pilot interviews of prior EOC patients. Questionnaire development was an iterative process, with care taken to provide a balanced instrument mindful of completion time requirement. Questions focused on factors hypothesized to be associated with decision regret, and reflections of satisfaction developed ad hoc to achieve the study objectives. Survey items were tested thoroughly in a small sample of volunteer patients and topic experts before distribution.

The following domains were examined in 30 items: demographics (10 questions), perceived adequacy of information and emotional support (2 questions), reproductive planning (6 questions), desire for parenthood (3 questions), satisfaction (4 questions), and decision regret (5 questions). Likert-type scales were used. Percentage estimations were offered via multiple choice response in intervals of 10% (Supplemental Appendix).

Demographics

Basic demographics included relationship status, education, income, race and sexual orientation. Participants were asked whether, "Work covered at least some expenses to freeze my eggs" (Y/N), to determine employer benefit status (Supplemental Appendix). Data regarding oocyte yield, number of retrieval cycles, anti-müllerian hormone and antral follicle counts were derived from the electronic medical record.

Perceived Adequacy of Information and Emotional Support

Using Likert-type scales, perceived adequacy of information ("I had enough information when I decided to freeze eggs"), and perceived adequacy of emotional support ("I felt adequate emotional support during the process") were assessed.

Reproductive Planning

Likelihood of using frozen eggs. Participants were asked to estimate the likelihood they would return to use their eggs to achieve pregnancy, using multiple-choice options of 0–100% in 10% intervals.

Predicted chances of a live birth using frozen eggs. To evaluate women's perception of achieving a live birth using their frozen oocytes, participants were asked, "With the number of eggs you have frozen, what do you think are your chances of having a baby by IVF?" Participants were also asked to indicate the number of babies they expected using banked eggs. Expectations of live birth rates per oocyte were derived from these responses.

Latest age preferred for childbearing. To characterize reproductive attitudes, participants were asked, “What is the latest age at which you could see yourself having a baby?”

Subsequent pregnancy. Participants were asked whether they had delivered a baby since EOC, and, if so, the method of achieving pregnancy.

Desire for parenthood. Three questions from the validated Fertility Problem Inventory (FPI) “Need for Parenthood” and “Rejection of Childfree Lifestyle” domains (15) were selected to measure the strength of the desire for parenthood, with higher values indicating greater strength of desire. An FPI Parenting Score was derived as the numeric average of the coded responses to these three questions, after reversing the negatively phrased item.

Satisfaction. Questions regarding satisfaction sentiments specific to the EOC intervention were designed by the investigators to allow insights into the nature of satisfaction following the EOC intervention. Using Likert-type scales, participants reflected on the following items: “I feel like I have more control over my reproductive future,” “I feel like I have more flexibility in planning a family,” “I feel like I have more options for planning a family,” and “If I never use my eggs to get pregnant, I will still be happy I did it.”

Decision regret. Decision regret was measured with the Decision Regret Scale (DRS) (11). The DRS is a five-item validated self-report instrument, designed to measure regret related to health care decision making (11). The DRS has been validated in numerous patient populations and has well-established internal consistency (Cronbach alpha = 0.81–0.95 across 25 studies) (12). The scoring algorithm yields scores from 0–100, with 0 indicating absent regret and 100 indicating extreme regret (11). DRS scores were interpreted as follows: 0, no regret; 1–25, mild regret; and >25, moderate to severe regret.

Statistical Analysis

Descriptive statistics were generated and tested for normality. Spearman correlation assessed the relationship between oocytes frozen and DRS scores. An age-adjusted logistic regression model was used to evaluate the impact of banking in the lowest quartile of eggs (i.e. ≤ 10 oocytes frozen) compared to all other women. Likert-type scale responses, considered as possible predictors, were coded from 1–5, to reflect strongly disagree to strongly agree, respectively. Percent estimations, considered in 10% intervals from 0–100%, were coded from 0 to 10. DRS scores were considered dichotomously, with scores >25 indicative of moderate to severe regret. Univariate logistic regression analyses identified factors associated with the primary outcome, moderate to severe decision regret. Multivariate regression models were generated using factors meeting significance of $P < .10$ in the univariate analysis. DRS scores were further considered as a continuous outcome in ancillary linear regression analyses. Due to co-linearity between number of eggs frozen and predicted probability of live birth with the number of eggs frozen, models were analyzed with these factors considered individually; the final model included the latter. Self-reports of frozen eggs banked were

considered in lieu of laboratory inventory in the regression models. Correction for multiple comparisons was not performed, given the exploratory nature of this analysis. Statistical analyses were performed using STATA v14.2 (Stata Corp.).

RESULTS

Of the 503 survey invitations distributed via email, 16 were undeliverable, and one invitee replied declining to participate. From the 487 delivered invitations, 201 women (41.3%) responded. Follow-up time interval from EOC to survey submission averaged 2.04 years (range 0.32–5.67 y).

Respondents and non-respondents did not differ on the basis of age at time of oocyte cryopreservation (36.5 vs. 36.8 y, $P = .20$), years elapsed since freezing oocytes (2.04 vs. 1.98, $P = .50$), antral follicle count (12.8 vs. 11.7, $P = .26$), or number of eggs banked (16.3 vs. 15.0, $P = .13$).

Demographics

Demographics of respondents are provided in Table 1. Mean age was 36.5 years (range 24.7–44.0 y); most women (70%) were age 34–40 years at time of egg banking. The majority of respondents (63%) were Caucasian, highly educated (78% graduate or professional degree), and reported relatively high household incomes (66% >\$100,000) (Table 1). At the time of EOC, 28 women (14%) reported a previous pregnancy; only one pregnancy (1%) had resulted in live birth.

Seventy-two percent of women ($n = 145$) underwent a single retrieval for EOC (Table 1). Median number of total eggs banked was 15 (interquartile range 11–21, range 1–58). Considering the first EOC cycle only, a median of 12 oocytes were frozen (range 1–44). Overall, women accurately recalled the number of oocytes they had frozen ($r = 0.92$, $P < .001$).

Twelve women (6%) returned to use their eggs to achieve pregnancy. Five of these women (2%) had a resultant live birth by the time of the survey. Eighteen additional women reported live births in the interval between EOC and survey response (23 [11%] total women with live births; 16 of these [8%] occurred naturally, and 2 [1%] required intrauterine insemination).

Perceived Adequacy of Information and Emotional Support

Most women (80%) agreed they had adequate information when deciding to bank eggs. However, 27 women (14%) disagreed; the remaining (6%) were neutral. Similarly, while the majority of women (69%) perceived adequate emotional support during EOC, 27 women (14%) did not; and 33 women (17%) felt neutral.

Reproductive Planning

Estimates regarding the likelihood of returning to use banked eggs for pregnancy varied widely (range 0–100%); 50% was the most common response (34% of respondents) (Supplemental Fig. 1). Mean patient-estimated probability

TABLE 1**Demographics of survey respondents.**

Variable	% (n)
Age (y) at time of EOC (n=201)	
≤30	2 (5)
30–32	4 (9)
32–34	11 (22)
34–36	22 (45)
36–38	27 (56)
38–40	21 (43)
40–42	8 (16)
≥42	2 (5)
Education level (n=201)	
Some college	1 (1)
Bachelor's degree	22 (44)
Graduate or professional degree	78 (156)
Race/ethnicity (n=195)	
White	63 (123)
Asian	24 (47)
Hispanic	3 (5)
Multi-ethnic	6 (12)
Other	4 (8)
Relationship status	
Single	76 (152)
Significantly involved	16 (33)
Living with a partner	7 (14)
Married	1 (2)
Household income, \$ (n=201)	
<50,000	6 (11)
50,000–100,000	22 (44)
100,000–250,000	56 (113)
250,000–500,000	8 (17)
>500,000	2 (5)
Prefer not to state	5 (11)
Sexual orientation (n=196)	
Heterosexual	96 (189)
Lesbian	1 (1)
Bisexual	2 (4)
Prefer not to state	1 (2)
Employer covered cost of EOC (n=200)	24 (48)
Number of egg retrievals (n=201)	
1	71 (143)
2	24 (47)
3	4 (8)
4	2 (3)
Total number of eggs frozen (n=201)	
<10	18 (37)
10–20	51 (102)
20–30	19 (39)
30–40	8 (17)
>40	3 (6)

Note: Demographic parameters reflect characteristics at time of elective oocyte cryopreservation (EOC).

Greenwood. Decision regret after social egg freezing. *Fertil Steril* 2018.

of achieving a live birth with their banked eggs was 56% (range 0–100%, SD 26%). Mean estimated probability of live birth per oocyte frozen was 5.9% (range 0.5%–25.7%, SD 4.2%). The latest age at which you could see yourself having a baby was 43.2 years on average (range 34.0–65.0).

Desire for Parenthood

Attitudes about the importance of parenting also varied. Ninety-six women (50%) disagreed with the statement, “I could visualize a happy life without a child.” One hundred fifteen women (59%) agreed, “as long I can remember, I’ve wanted to be a parent.” The most common single response

to the sentiment, “for me, being a parent is a more important goal than having a satisfying career” was “neutral” (38%), followed by “agree” (33%), then “disagree” (14%).

Satisfaction

Qualitative attitudes reflecting satisfaction following EOC were queried. One hundred sixty-seven women (88%) perceived increased control over reproductive planning, and 159 (81%) perceived increased flexibility with family planning. The majority of women (88%) felt they had more options for planning a family following EOC. One hundred eighty-three respondents (89%) affirmed they will be happy they froze eggs, even if they never use them.

Decision Regret

Of the 201 respondents, 102 (51%) had no decision regret, 66 (33%) had mild, and 33 (16%) had moderate to severe decision regret. Median DRS score was 0 (interquartile range 0–15) and the mean was 10 (range 0–90), indicating a generally low prevalence of regret (Fig. 1).

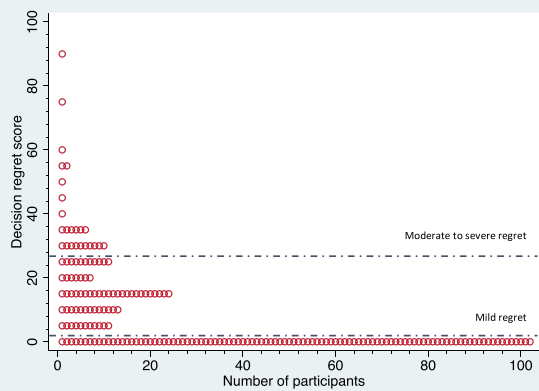
The relationship between DRS scores and number of oocytes cryopreserved was examined using Spearman’s rank correlation (Fig. 2). An inverse correlation was noted (Spearman’s $\rho = -0.27$, $P = .01$), suggesting increasing regret with lower numbers of cryopreserved oocytes. An age-adjusted logistic regression model identified a 4.0-fold increase in odds of decision regret in participants freezing ≤ 10 oocytes (representing the 25th percentile of banked eggs) compared with participants freezing >10 oocytes (adjusted odds ratio [OR] 4.0, 95% confidence interval [CI] 1.8, 8.8; $P < .001$).

Univariate logistic regression analysis identified the following variables associated with moderate to severe decision regret (DRS score >25): number of oocytes frozen, perceived adequacy of information when deciding to pursue EOC, perceived adequacy of emotional support during the EOC process, and patient-estimated probability of achieving a live birth using the banked eggs (Table 2). Age, time elapsed since EOC, income, whether an employer covered expenses, latest preferred age of childbearing, prior pregnancy, the occurrence of live birth since EOC, and the method of achieving a pregnancy following EOC were not associated with decision regret.

The multivariate logistic regression model included all the factors with significance level of $P < .10$ in the univariate analysis (Table 2). Of these factors, perceived adequacy of information when deciding to pursue EOC and patient-estimated probability of achieving a live birth with their frozen eggs retained independent, statistically significant associations with regret. On average, with each increasing level of agreement on the Likert scale, perceived adequate information reduced the odds of decision regret by 37% (OR 0.63, 95% CI 0.42–0.97, $P = .03$). Each 10% increase in patient-estimated probability of having a baby with their frozen eggs was associated with a 20% reduction in odds of decision regret (OR 0.80, 95% CI 0.67–0.96, $P = .01$) (Table 2).

To assess the impact of risk factors on magnitude of change in DRS scores, we also considered DRS scores as a

FIGURE 1

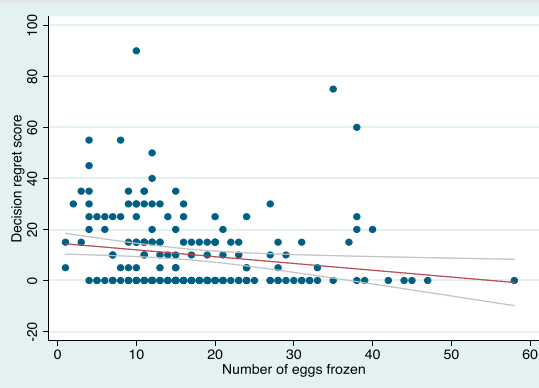


Decision Regret Scale (DRS) scores after elective oocyte cryopreservation. Increasing scores indicate higher levels of regret. Regret categories are indicated as follows: 0, no regret; 1–25, mild regret; and >25, moderate to severe regret; *dashed lines*, category thresholds.

Greenwood. Decision regret after social egg freezing. *Fertil Steril* 2018.

continuous outcome variable (Supplemental Table 1). Univariate linear regression models identified the same risk factors for decision regret as the logistic models, and additionally identified increasing patient-estimated likelihood of returning to use banked eggs for pregnancy as a factor associated with lower DRS scores. In a similarly constructed multivariate linear regression model, in addition to those factors identified in the multivariate logistic model, perceived adequacy of emotional support and patient-estimated likelihood of using the eggs to achieve pregnancy were significantly associated with DRS scores. On average, with each increasing point on the Likert scale, perceived adequate information was associated with a reduction in DRS score by 2.9 points (coeff -2.9 , 95% CI -5.1 to -0.8 , $P < .01$), and perceived adequate emotional support with a 2.1 points reduction in regret score

FIGURE 2



Correlation between number of oocytes frozen and decision regret score. *Red line*, linear fit model; *gray lines*, 95% confidence intervals Spearman's rho -0.27 , $P < .01$.

Greenwood. Decision regret after social egg freezing. *Fertil Steril* 2018.

(95% CI -4.3 to -0.0 , $P = .05$). Each 10% increase in patient-estimated likelihood of returning to use their eggs to achieve pregnancy was associated with a reduction in DRS score by 1.3 points (95% CI -2.1 to -0.5 , $P < .01$); while each 10% increase in patient-estimated probability of a successful live birth with their banked eggs was associated with a 1.1 points reduction in regret score (95% CI -1.9 to -0.3 , $P < .01$).

DISCUSSION

As new technologies for family planning emerge, unintended consequences may result. Decision regret is one potential negative outcome that may result from the emergent, rapid uptake of elective oocyte cryopreservation, as women seek to counteract age-related fertility decline (2).

At present, the professional guidelines of the American Society for Reproductive Medicine ASRM caution “marketing [oocyte cryopreservation] technology for the purpose of deferring childbearing may give women false hope and encourage women to delay childbearing” (1). The position of the ASRM explicitly cites the lack of data regarding the emotional risks of EOC. Outcomes data regarding decision regret and the ultimate life impact of EOC are needed to inform counseling of patients about potential risks and expectations. Like contraceptive choice, oocyte cryopreservation may enhance reproductive control. Decision regret is an important consideration that has been well-characterized for other reproductive choices such as sterilization procedures (16), and similarly warrants attention in EOC.

Interpretation of our decision regret data is complex. Mean DRS score in our study was 10, which is lower than the mean of 17 reported in a recent systematic review of 44 studies across a number of clinical populations making a variety of healthcare decisions (12). Positive perceptions of enhanced reproductive control, flexibility and options prevailed, indicating high levels of satisfaction; this report extends prior work characterizing “empowerment” following EOC (9). However, our findings also elucidate critical concerns. One in two women (49%) had some degree of decision regret following this purely elective intervention. One in six women (16%) had evidence of moderate to severe regret, providing an opportunity to examine factors associated with this outcome.

Women who had lower numbers of oocytes cryopreserved were significantly more likely to experience regret, as we hypothesized. Specifically, participants in the lowest quartile of total eggs banked (≤ 10 oocytes) were at 4-fold increased odds of regret compared to those freezing >10 oocytes. The counseling of patients considering EOC should include a discussion of the risk of regret and its potential relationship to number of oocytes retrieved. Clinicians should help guide appropriate expectations, taking into account established predictors of oocyte yield (antral follicle count or anti-mullerian hormone), available data on age-specific aneuploidy rates in IVF (17), expected live birth rates per frozen oocyte (3, 18), and the financial implications of potentially requiring >1 cycle to achieve a satisfying number of eggs.

It is possible that patients who have lower numbers of oocytes retrieved might interpret this as a sign of low fertility or

TABLE 2

Univariate and multivariate logistic regression analyses of variables associated with decision regret.

Variable	Model 1: unadjusted OR		Model 2: aOR	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (y) at time of EOC	1.03 (0.91, 1.17)	.61		
Age (y) now	0.99 (0.89, 1.10)	.89		
Time (y) elapsed since EOC	0.76 (0.54, 1.06)	.11		
Employer benefit covers EOC cost	0.87 (0.34, 2.15)	.76		
Eggs frozen, n	0.94 (0.90, 0.99)	.02		
Adequacy of information prior to EOC	0.58 (0.41, 0.82)	< .01	0.63 (0.42, 0.97)	.03
Adequacy of emotional support during EOC	0.58 (0.41, 0.81)	< .01	0.74 (0.49, 1.11)	.15
Likelihood of using eggs	0.86 (0.73, 1.02)	.08	0.85 (0.70, 1.03)	.10
Predicted chances of live birth using frozen eggs	0.81 (0.70, 0.95)	< .01	0.80 (0.67, 0.96)	.01
FPI Parenting Score	0.66 (0.43, 1.00)	.05	0.83 (0.51, 1.36)	.47
Live birth following EOC	0.84 (0.23, 3.02)	.79		
Latest age (y) preferred for childbearing	1.05 (0.93, 1.18)	.43		

Note: Decision regret is indicated by Decision Regret Scale (DRS) score >25. aOR = adjusted odds ratio; CI = confidence interval; EOC = elective oocyte cryopreservation; FPI = fertility problem inventory; OR = odds ratio.

Greenwood. Decision regret after social egg freezing. *Fertil Steril* 2018.

impending infertility, which evokes distress and increases regret. Patient conflation of number of oocytes retrieved in an EOC cycle with fertility status is a potential hazard of this intervention. Anti-mullerian hormone (AMH) levels, a close correlate of number eggs retrievable during a stimulation protocol, has recently been shown to lack predictive value for time to spontaneous pregnancy (19), and cannot distinguish between a cohort of women with unexplained infertility from healthy community controls (20). Thus, number of oocytes banked may also lack predictive value of “fertility status”. Rigorous longitudinal studies are needed to inform attempts at reproductive forecasting (21). Physicians should take care to counsel patients appropriately regarding implications EOC cycle results for their future fertility.

Women who perceived lower adequacy of information and emotional support during the treatment process were significantly more likely to experience regret. These risk factors are potentially modifiable. Patients might benefit from additional informational resources about the stimulation procedure, a thorough discussion of risks, and available data regarding anticipated medical outcomes using cryopreserved oocytes (22, 23). Reflections of other women who froze eggs for social reasons might augment perceived preparation. Emphasis should be placed on resources for emotional support during the treatment process, as this factor is associated with mitigated regret. Individuals with low markers of ovarian reserve (specifically antral follicle counts or anti-mullerian hormone level) might warrant additional support prior to and during the stimulation process, as these measures have been shown to correlate with oocyte yield.

Non-modifiable risk factors for increased regret include number of oocytes retrieved, and probability of a live birth,

which is a function of oocyte number and age. These factors should be acknowledged upfront in counseling patients.

Women who thought they were more likely to use their banked eggs were less likely to regret their decision, according to the linear model. Neither modifiable nor non-modifiable per se, this risk factor is unpredictable and at the core of the potential promise of EOC. While models assessing the efficacy and cost-effectiveness of oocyte cryopreservation have been described (24), a personalized decision algorithm which differentially weights benefits and disadvantages is necessary.

Personal attitudes around the desire for parenthood, reflected in the derived FPI Parenting Score, were associated with decision regret in the univariate analysis at borderline statistical significance; this association was abolished the multivariate analysis. In addition, whether EOC costs were covered by an employer benefit was not associated with decision regret in our study, contrary to our expectation.

Of note, our results highlight the potential issue of unrealistic expectations for success following EOC. Although the average estimate of live birth per oocyte banked (5.9%) was consistent with available publications (3, 18), 13 women (6%) ages 34.3 – 40.6 years who banked between 10 – 34 eggs estimated their likelihood of having a baby at 100%. The presence of such unrealistic expectations might temporarily and artificially reduce decision regret in the short-term, but ultimately intensify regret in the long-term if banked oocytes do not yield a take-home baby. The role of “anticipatory regret” may provide some explanation for falsely inflated expectations. Defined as the fear of “remorse later in life [for] not taking any action,” anticipatory regret was underscored in a qualitative study of 20 women on the waiting list for elective oocyte cryopreservation at a Dutch university center in 2012 (25). In this study, “anticipatory

regret" (i.e. fearing future regret for not pursuing action to preserve fertility) contributed to a re-interpretation of the estimated effectiveness and risks of egg freezing (25). Physicians should be acutely aware of the potential for unrealistic expectations, and are obligated to emphasize realistic limitations of egg freezing technology during patient counseling, to mitigate the risk of future disappointment or regret.

Overall, prevalence of regret in our study exceeded those previously reported at 0% in a telephone-based survey study (14). This might reflect the more rigorous, validated DRS instrument we used to measure regret, which examines five aspects of decision regret and offers five Likert-type responses; in contrast, the prior study asked "Do you regret to have frozen oocytes?" and allowed stratified yes/no/don't know responses. In addition, our data is derived from an instrument administered online rather than a physician-conducted interview over the phone; the latter design might inhibit honesty.

Finally, it is notable that women in this cohort accepted the option of childbearing at advanced maternal age (average 43.2 years). The natural history of a decision to delay childbearing via EOC is, inherently, advancing maternal age. Counseling regarding the risks of pregnancy at an advanced maternal age cannot be overlooked in patient counseling; these risks might further impact decision regret.

Strengths, Limitations and Future Directions

Strengths of our study include the large number of participants who had a follow-up interval of several years. We used a validated instrument to analyze decision regret. Surveys were completed online, offering a private, remote setting which might promote honesty.

Our study has several limitations. The retrospective methodology introduced potential bias due to cognitive dissonance (26) and recall (27); however a retrospective design is required to address the primary study question. Variable and relatively short follow-up duration is another limitation. Although time elapsed since treatment was not associated with DRS scores in our analyses, only 12 women returned to attempt pregnancy with their frozen eggs, constraining our ability to assess the impact of failure to achieve a live birth with one's frozen eggs. Unrealistic expectations might contribute to low levels of regret short-term. Longer term studies to evaluate regret over many years following EOC are greatly needed. In addition, we did not ask patients to recall their physician's counseling regarding anticipated success rates, which could help identify potential discordance with their expectations. Our regression analysis identified associations between various sentiments and decision regret at follow up, rather than predictors per se. The causal direction cannot be imputed; while adequate information or emotional support might predict decision satisfaction, the reverse relationship (i.e. feeling unsatisfied with the outcome of EOC for extraneous reasons might invoke recollection of poor preparation or emotional support) may conversely be true. Responses reflect the attitudes of a geographically limited population, generally highly-educated Caucasian women of high socioeconomic status in the San Francisco Bay Area, motivated to respond.

Future studies employing open-ended questions to target both the etiology of regret and opportunities for regret prophylaxis in future women are warranted. Prospective studies which catalogue impressions of informational preparedness, expectations, and emotional support in real time might further clarify these important issues. Longitudinal studies over a longer follow-up period are critical to better assess the impact of returning to use eggs to attempt pregnancy, and the sequelae of these attempts, on decision regret. Although subsequent live birth following EOC and method of achieving pregnancy were not associated with regret in our analysis, the numbers were too small to provide meaningful conclusions. The concern exists that EOC might impact subsequent reproductive choices and behaviors, result in compromised outcomes, and create regret. Longer-term studies will fill in the current gaps in knowledge, evaluate the ongoing concern of "false hope," and enable evidence-based counseling by clinicians.

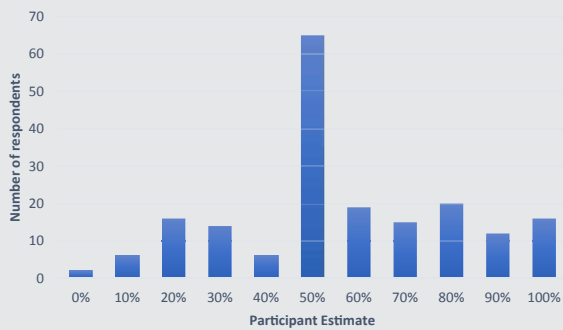
CONCLUSIONS

In conclusion, there is a non-negligible risk of decision regret following EOC. Drivers of decision regret include number of cryopreserved oocytes, anticipated success in achieving a live birth with cryopreserved oocytes, perceived adequacy of information prior to undergoing EOC, and perceived adequacy of emotional support during the EOC process. Buttressing preparatory information and emotional support resources might alleviate decision regret. Prevailing sentiments of increased reproductive control and flexibility, and happiness irrespective of future oocyte usage, suggest intangible benefits. As oocyte cryopreservation technologies are increasingly deployed for elective indications, additional studies are warranted to assess long-term outcomes, to characterize potential harms including the possible impact of unrealistic expectations, and to understand how best to avoid such harms.

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SUPPLEMENTAL FIGURE 1

Estimated likelihood of returning to use oocytes for pregnancy. Responses to question 13, "What are the chances you come back to use your eggs to try to get pregnant (please take a guess)?"

Greenwood. Decision regret after social egg freezing. Fertil Steril 2018.